



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61L 25/00	A1	(11) International Publication Number: WO 99/10020 (43) International Publication Date: 4 March 1999 (04.03.99)
(21) International Application Number: PCT/US98/17708 (22) International Filing Date: 27 August 1998 (27.08.98) (30) Priority Data: 08/920,876 29 August 1997 (29.08.97) US (71) Applicant: CLOSURE MEDICAL CORPORATION [US/US]; 5250 Greens Dairy Road, Raleigh, NC 27616 (US). (72) Inventors: CLARK, Jeffrey, G.; 908 Bennington Drive, Raleigh, NC 27617 (US). LEUNG, Jeffrey, C.; 813 Berwyn Way, Raleigh, NC 27615 (US). (74) Agents: OLIFF, James, A. et al.; Oliff & Berridge, PLC, P.O. Box 19928, Alexandria, VA 22320 (US).		(81) Designated States: AU, BR, CA, CN, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: METHODS OF APPLYING MONOMERIC COMPOSITIONS EFFECTIVE AS WOUND CLOSURE DEVICES (57) Abstract A method of joining together <i>in vivo</i> living tissue surfaces includes (a) holding together at least two tissue surfaces to form abutted tissue surfaces; (b) applying across said abutted tissue surfaces an excessive amount of an adhesive composition comprising at least one monomer that forms a medically acceptable polymer with an applicator having a porous applicator tip; and (c) maintaining said tissue surfaces in contact <i>in vivo</i> until said composition polymerizes to form a thick film of polymerized composition on said abutted tissue surface.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

METHODS OF APPLYING MONOMERIC COMPOSITIONS EFFECTIVE AS
WOUND CLOSURE DEVICES

BACKGROUND OF THE INVENTION

1. Field of Invention

5 This invention relates to monomer and polymer compositions useful to form biomedical adhesives and sealants, and methods of applying them. More particularly, this invention relates to methods of applying monomer and polymer compositions and their use
10 for medical, surgical and other in vivo applications.

2. Description of Related Art

 Products in primary use for wound closure are surgical sutures and staples. Sutures are recognized to provide adequate wound support. However, sutures cause
15 additional trauma to the wound site (by reason of the need for the needle and suture to pass through tissue and the need to anesthetize the wound area via needle application) and are time-consuming to place, and, at skin level, can cause unattractive wound closure marks. Surgical staples
20 have been developed to speed wound apposition and provide improved cosmetic results. However, surgical staples also impose additional wound trauma and require the use of ancillary and often expensive devices for positioning and applying the staples. Both sutures and staples are
25 especially problematic in pediatric cases where the patient may have a strong fear response and refuse to cooperate with their placement, and in geriatric cases where the skin tissue is weaker and prone to tearing.

 Alternatively, adhesives have been proposed as
30 wound closure devices. One group of such adhesives is the monomeric forms of alpha-cyanoacrylates.

 Reference is made, for example, to U.S. Patents Nos. 5,328,687 to Leung et al; 3,527,841 to Wicker et al.; 3,722,599 to Robertson et al.; 3,995,641 to Kronenthal et
35 al.; and 3,940,362 to Overhults, which disclose alpha-cyanoacrylates that are useful as surgical adhesives. All

of the foregoing references are hereby incorporated by reference herein.

Typically, the cyanoacrylate surgical adhesive is applied to one or both surfaces of wounds or incisions, including the internal portions of the wound, with any excess adhesive being quickly removed from the bonding surfaces. Subsequently, the edges of the wound are held together until they adhere. See U.S. Patent No. 3,559,652 to Coover, Jr. et al. Two coatings of adhesive may be applied to the wound surfaces. However, this method of application produces significant levels of histotoxicity due to the surgical adhesive being trapped within the wound site.

An additional method of application of the cyanoacrylate surgical adhesive to wounds or incisions involves the formation of a bridge over the wound site. As described in U.S. Patent No. 3,667,472 to Halpern, the incised tissues are held together and maintained in fixed relationship until a cyanoacrylate adhesive has been applied over the incision and allowed the necessary time to develop a bond. Excess adhesive is removed from the incision. However, the composition utilized in this process suffers from inadequate film strength and flexibility with high histotoxicity in wound sites.

These conventional methods of application of tissue adhesive generally do not specify a particular method that is preferable, nor is there any mention of placing more than minimal amounts of glue upon wounds. The conventional application techniques strive to reduce application of excessive amounts of tissue adhesive to the wound due to histotoxicity.

A topical tissue adhesive commercially available is Histoacryl® available from B. Braun Melsungen AG of Germany. The manufacturer recommends use of this adhesive only for closure of minor skin wounds and not for internal use. Moreover the manufacturer recommends that the adhesive be used sparingly or in thin films because thick

films do not increase the film strength and can lead to necrosis of surrounding tissue due to thermogenic reaction. Moreover, films formed from this adhesive are brittle, permitting severe dehiscence of wounds.

5 Plasticizers have been added to cyanoacrylate surgical adhesive compositions. See, for example, U.S. Patents Nos. 3,759,264 to Coover, Jr. et al., 3,667,472 to Halpern, 3,559,652 to Banitt, the subject matter of which is incorporated herein by reference. However, the
10 incorporation of plasticizers in such compositions has led to decreased film strength of the polymerized material. Accordingly, such compositions have been utilized only within the wound site and not over the wound site as a bridge.

15 Other additives have been employed in cyanoacrylate surgical adhesives for the purposes of modifying the cure rate and shelf life of the adhesives. For example, cyanoacrylate polymerization inhibitors or stabilizers including Lewis acids, such as sulfur dioxide,
20 nitric oxide, boron trifluoride and other acidic substances, including hydroquinone monomethyl ether, hydroquinone, nitrohydroquinone, catechol and hydroquinone monoethyl ether. See, for example, U.S. Patent No. 3,559,652 to Banitt, the subject matter of which is
25 incorporated herein by reference. These compositions contain significant amounts of impurities and, thus, require substantial amounts of stabilizer to inhibit premature polymerization of the monomer.

Other adhesives include both plasticizers and
30 stabilizing agents. For example, U.S. Patent No. 5,480,935 to Greff et al. describes a tissue adhesive having a plasticizer and a polymerization inhibitor. However, the plasticizers disclosed therein (i.e., alkyl phthalates) are highly toxic and are not suitable for use
35 in biocompatible medical adhesives.

SUMMARY OF THE INVENTION

The present invention provides a process for application of a surgical adhesive composition in a bridge structure that provides an unexpectedly improved bond strength over conventional application techniques of the polymerized composition on the wound or incision site, which increases the effectiveness of monomers and polymers in in vivo applications. The surgical adhesive forms a flexible and strong bond over wounds and incisions. Moreover, the method of applying a surgical adhesive to a wound or incision provides a strong and flexible biocompatible bond. The present invention is also directed to methods of applying a monomeric composition with a porous applicator tip and with an applicator tip having a non-uniform distribution of initiator or rate modifier.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

One embodiment of the present invention provides a wound closure monomer composition, comprising:

- A) at least one monomer, which forms a medically acceptable wound closure polymer:
- B) at least one plasticizing agent; and
- C) at least one acidic stabilizing agent.

In other embodiments, the present invention is directed to methods of using the above-described monomers, copolymers and polymers made therefrom for biomedical purposes. See U.S. Patent Serial No. 08/609,921, incorporated in its entirety herein by reference.

In one such embodiment, the edges of a wound or incision are held together and an excessive amount of the above-described surgical adhesive composition is applied to the already pinched or abutted opposing wound edges, preferably utilizing more than one application stroke. This process forms a bridge over the abutted opposing wound edges that is flexible and possesses high tensile strength. The excessive amount of adhesive placed on the

abutted opposing wound edges forms a thick film thereon and unexpectedly increases film strength.

For example, the present invention includes a method of forming a biocompatible film across abutted tissue surfaces, comprising; (a) holding together at least two tissue surfaces to form abutted tissue surfaces, (b) applying across said abutted tissue surfaces an adhesive biocompatible monomer composition, and (c) allowing said composition to polymerize and form a biocompatible film on said abutted tissue surfaces having an in vivo film strength of at least 70 mmHg of vacuum pressure required to induce wound failure, generally from 70 mmHg to 400 mmHg of vacuum pressure required to induce wound failure, preferably from 90 mmHg to 400 mmHg of vacuum pressure required to induce wound failure, and more preferably from 100 mmHg to 400 mmHg of pressure required to induce wound failure.

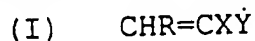
Preferably, the monomer is an alpha-cyanoacrylate. The monomer compositions of this invention and polymers formed therefrom are useful as tissue adhesives, sealants for preventing bleeding or for covering open wounds, and in other biomedical applications. They find uses in, for example, apposing surgically incised or traumatically lacerated tissues; retarding blood flow from wounds; and aiding repair and regrowth of living tissue.

As above-mentioned, conventional surgical adhesive compositions have included plasticizers with the adverse effect of reducing the film strength. It has been discovered that, contrary to prior belief, the film strength (e.g., toughness) under certain conditions is not adversely reduced upon the addition of greater amounts of plasticizing agent. Depending on the particular acidic stabilizing agent and the purity of the monomer utilized in the adhesive composition, the addition of greater amounts of plasticizing agent may increase the toughness of the resulting bond formed on the wound. It has been discovered that weak acidic stabilizing agents do not

significantly affect the polymerization of the monomer in the present composition and provide increased film strength with increasing amounts of plasticizing agents.

Monomers that may be used in this invention are readily polymerizable, e.g. anionically polymerizable or free radical polymerizable, to form polymers. Such monomers include those that form polymers, which may, but do not need to, biodegrade. Reference is made, for example, to U.S. Patent No. 5,328,687, which is hereby incorporated by reference herein. As defined herein, "histotoxicity" refers to adverse tissue response, such as inflammation due to the presence of toxic materials in the tissue.

Useful 1,1-disubstituted ethylene monomers include, but are not limited to, monomers of the formula:



wherein X and Y are each strong electron withdrawing groups, and R is H, $-\text{CH}=\text{CH}_2$ or, provided that X and Y are both cyano groups, a $\text{C}_1\text{-C}_4$ alkyl group.

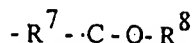
Examples of monomers within the scope of formula (I) include alpha-cyanoacrylates, vinylidene cyanides, $\text{C}_1\text{-C}_4$ alkyl homologues of vinylidene cyanides, dialkyl methylene malonates, acylacrylonitriles, vinyl sulfinates and vinyl sulfonates of the formula $\text{CH}_2=\text{CX}'\text{Y}'$ wherein X' is $-\text{SO}_2\text{R}'$ or $-\text{SO}_3\text{R}'$ and Y' is $-\text{CN}$, $-\text{COOR}'$, $-\text{COCH}_3$, $-\text{SO}_2\text{R}'$ or $-\text{SO}_3\text{R}'$, and R' is H or hydrocarbyl.

Preferred monomers of formula (I) for use in this invention are alpha-cyanoacrylates. These monomers are known in the art and have the formula



wherein R^2 is hydrogen and R^3 is a hydrocarbyl or substituted hydrocarbyl group; a group having the formula $-\text{R}^4\text{-O-R}^5\text{-O-R}^6$, wherein R^4 is a 1,2-alkylene group having 2-4 carbon atoms, R^5 is an alkylene group having 2-4 carbon

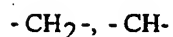
atoms, and R^6 is an alkyl group having 1-6 carbon atoms; or



a group having the formula $\begin{array}{c} || \\ O \end{array}$, wherein R^7 is



$\begin{array}{c} | \\ -C(CH_3)_2- \end{array}$, or $-C(CH_3)_2-$ and R^8 is an organic radical.



Examples of suitable hydrocarbyl and substituted hydrocarbyl groups include straight chain or branched chain alkyl groups having 1-16 carbon atoms; straight chain or branched chain C_1 - C_{16} alkyl groups substituted with an acyloxy group, a haloalkyl group, an alkoxy group, a halogen atom, a cyano group, or a haloalkyl group; straight chain or branched chain alkenyl groups having 2 to 16 carbon atoms; straight chain or branched chain alkynyl groups having 2 to 12 carbon atoms; cycloalkyl groups; aralkyl groups; alkylaryl groups; and aryl groups.

The organic radical R^8 may be substituted or unsubstituted and may be straight chain, branched or cyclic, saturated, unsaturated or aromatic. Examples of such organic radicals include C_1 - C_8 alkyl radicals, C_2 - C_8 alkenyl radicals, C_2 - C_8 alkynyl radicals, C_3 - C_{12} cycloaliphatic radicals, aryl radicals such as phenyl and substituted phenyl and aralkyl radicals such as benzyl, methylbenzyl and phenylethyl. Other organic radicals include substituted hydrocarbon radicals, such as halo(e.g., chloro-, fluoro- and bromo-substituted hydrocarbons) and oxy-(e.g., alkoxy substituted hydrocarbons) substituted hydrocarbon radicals. Preferred organic radicals are alkyl, alkenyl and alkynyl radicals having from 1 to about 8 carbon atoms, and halo-substituted derivatives thereof. Particularly preferred are alkyl radicals of 4 to 6 carbon atoms.

In the cyanoacrylate monomer of formula (II), R^3 is preferably an alkyl group having 1-10 carbon atoms or a group having the formula $-AOR^9$, wherein A is a divalent

straight or branched chain alkylene or oxyalkylene radical having 2-8 carbon atoms, and R^9 is a straight or branched alkyl radical having 1-8 carbon atoms.

5 Examples of groups represented by the formula $-AOR^9$ include 1-methoxy-2-propyl, 2-butoxy ethyl, isopropoxy ethyl, 2-methoxy ethyl, and 2-ethoxy ethyl.

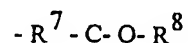
The preferred alpha-cyanoacrylate monomers used in this invention are 2-octyl cyanoacrylate, dodecyl cyanoacrylate, 2-ethylhexyl cyanoacrylate, butyl
10 cyanoacrylate, methyl cyanoacrylate, 3-methoxybutyl cyanoacrylate, 2-butoxyethyl cyanoacrylate, 2-isopropoxyethyl cyanoacrylate, or 1-methoxy-2-propyl cyanoacrylate.

The alpha-cyanoacrylates of formula (II) can be
15 prepared according to methods known in the art. Reference is made, for example, to U.S. Patents Nos. 2,721,858 and 3,254,111, each of which is hereby incorporated by reference herein. For example, the alpha cyanoacrylates can be prepared by reacting an alkyl cyanoacetate with
20 formaldehyde in a non-aqueous organic solvent and in the presence of a basic catalyst, followed by pyrolysis of the anhydrous intermediate polymer in the presence of a polymerization inhibitor. The alpha-cyanoacrylate monomers prepared with low moisture content and
25 essentially free of impurities are preferred for biomedical use.

The alpha-cyanoacrylates of formula (II) wherein R^3 is a group having the formula $-R^4-O-R^5-O-R^6$ can be prepared according to the method disclosed in U.S. Patent
30 No. 4,364,876 to Kimura et al., which is hereby incorporated by reference herein. In the Kimura et al. method, the alpha-cyanoacrylates are prepared by producing a cyanoacetate by esterifying cyanoacetic acid with an alcohol or by transesterifying an alkyl cyanoacetate and
35 an alcohol; condensing the cyanoacetate and formaldehyde or para-formaldehyde in the presence of a catalyst at a molar ratio of 0.5-1.5:1, preferably 0.8-1.2:1, to obtain

a condensate; depolymerizing the condensation reaction mixture either directly or after removal of the condensation catalyst to yield crude cyanoacrylate; and distilling the crude cyanoacrylate to form a high purity cyanoacrylate.

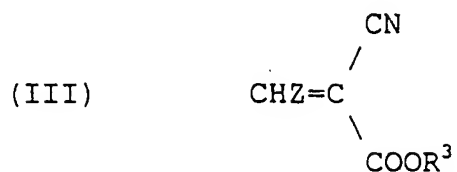
The alpha-cyanoacrylates of formula (II) wherein



R^3 is a group having the formula $\begin{array}{c} || \\ || \\ O \end{array}$ can be prepared

according to the procedure described in U.S. Patent No. 3,995,641 to Kronenthal et al., which is hereby incorporated by reference herein. In the Kronenthal et al. method, such alpha-cyanoacrylate monomers are prepared by reacting an alkyl ester of an alpha-cyanoacrylic acid with a cyclic 1,3-diene to form a Diels-Alder adduct which is then subjected to alkaline hydrolysis followed by acidification to form the corresponding alpha-cyanoacrylic acid adduct. The alpha-cyanoacrylic acid adduct is preferably esterified by an alkyl bromoacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct. Alternatively, the alpha-cyanoacrylic acid adduct may be converted to the alpha-cyanoacrylyl halide adduct by reaction with thionyl chloride. The alpha-cyanoacrylyl halide adduct is then reacted with an alkyl hydroxyacetate or a methyl substituted alkyl hydroxyacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct or carbalkoxy alkyl alpha-cyanoacrylate adduct, respectively. The cyclic 1,3-diene blocking group is finally removed and the carbalkoxy methyl alpha-cyanoacrylate adduct or the carbalkoxy alkyl alpha-cyanoacrylate adduct is converted into the corresponding carbalkoxy alkyl alpha-cyanoacrylate by heating the adduct in the presence of a slight deficit of maleic anhydride.

Examples of monomers of formula (II) include cyanopentadienoates and alpha-cyanoacrylates of the formula:



5

wherein Z is $-\text{CH}=\text{CH}_2$ and R^3 is as defined above. The monomers of formula (III) wherein R^3 is an alkyl group of 1-10 carbon atoms, i.e., the 2-cyanopenta-2,4-dienoic acid esters, can be prepared by reacting an appropriate 2-cyanoacetate with acrolein in the presence of a catalyst such as zinc chloride. This method of preparing 2-cyanopenta-2,4-dienoic acid esters is disclosed, for example, in U.S. Patent No. 3,554,990, which is hereby incorporated by reference herein.

15

Preferred monomers are alkyl alpha-cyanoacrylates and more preferably octyl alpha-cyanoacrylates, especially 2-octyl alpha-cyanoacrylate. Monomers utilized in the present application should be very pure and contain few impurities (e.g., surgical grade).

20

Component B) of the compositions of this invention is at least one plasticizing agent that imparts flexibility to the polymerized monomer formed on the wound or incision. The plasticizing agent preferably contains little or no moisture and should not significantly affect the polymerization of the monomer.

25

Examples of suitable plasticizers include acetyl tributyl citrate, dimethyl sebacate, triethyl phosphate, tri(2-ethylhexyl)phosphate, tri(p-cresyl) phosphate, glyceryl triacetate, glyceryl tributyrate, diethyl sebacate, dioctyl adipate, isopropyl myristate, butyl stearate, lauric acid, trioctyl trimellitate, dioctyl glutarate and mixtures thereof. Preferred plasticizers are tributyl citrate and acetyl tributyl citrate.

30

Component C) of the compositions of this invention is at least one acidic stabilizing agent that inhibits polymerization. Such stabilizing agents may also include mixtures of anionic stabilizing agents and radical stabilizing agents.

35

Examples of suitable anionic stabilizing agents include sulfur dioxide, sulfonic acid, lactone, boron trifluoride, organic acids, alkyl sulfate, alkyl sulfite, 3-sulfolene, alkylsulfone, alkyl sulfoxide, mercaptan, and alkyl sulfide and mixtures thereof. Preferable anionic stabilizing agents are acidic stabilizing agents of organic acids such as acetic acid or phosphoric acid with acetic acid being a more preferable acidic stabilizing agent. The maximum amount of sulfur dioxide present in the adhesive composition should be less than 50 ppm, and preferably less than 30 ppm.

Examples of suitable radical stabilizing agents include hydroquinone, hydroquinone monomethyl ether, catechol, pyrogallol, benzoquinone, 2-hydroxybenzoquinone, p-methoxy phenol, t-butyl catechol, butylated hydroxy anisole, butylated hydroxy toluene, and t-butyl hydroquinone.

Suitable acidic stabilizing agents include those having pK_a ionization constants ranging from about 0 to about 7, preferably from about 1 to about 6, and more preferably from about 2 to about 5.5. For example, suitable acidic stabilizing agents include: hydrogen sulfide (pK_a 7.0), carbonic acid (pK_a 6.4), triacetylmethane (pK_a 5.9), acetic acid (pK_a 4.8), benzoic acid (pK_a 4.2), 2,4-dinitrophenol (pK_a 4.0), formic acid (pK_a 3.7), nitrous acid (pK_a 3.3), hydrofluoric acid (pK_a 3.2), chloroacetic acid (pK_a 2.9), phosphoric acid (pK_a 2.2), dichloroacetic acid (pK_a 1.3), trichloroacetic acid (pK_a 0.7), 2,4,6-trinitrophenol (picric acid) (pK_a 0.3), trifluoroacetic acid (pK_a 0.2), and mixtures thereof.

When adding the above-mentioned weak acidic stabilizing agents to the adhesive composition, it has been discovered that the addition of plasticizing agents in amounts ranging from about 0.5 wt.% to about 16 wt.%, preferably from about 3 wt.% to about 9 wt.%, and more preferably from about 5 wt.% to about 7 wt.% provides increased film strength (e.g., toughness) of the

polymerized monomer over polymerized monomers having amounts of plasticizing agents and acidic stabilizing agents outside of the above ranges.

5 The concentration of the acidic stabilizing agents utilized may vary depending on the strength of the acid. For example, when using acetic acid, a concentration of 80-200 ppm (wt/wt), preferably 90-180 ppm (wt/wt), and more preferably 100-150 ppm (wt/wt) may be utilized. When using a stronger acid, such as phosphoric acid a
10 concentration range of 20-80 ppm (wt/wt), preferably, 30-70 ppm (wt/wt) and more preferably 40-60 ppm (wt/wt) may be utilized.

The compositions of this invention may also include at least one biocompatible agent effective to
15 reduce active formaldehyde concentration levels produced during in vivo biodegradation of the polymer (also referred to herein as "formaldehyde concentration reducing agents"). Preferably, this component is a formaldehyde scavenger compound. Examples of formaldehyde scavenger
20 compounds useful in this invention include sulfites; bisulfites; mixtures of sulfites and bisulfites; ammonium sulfite salts; amines; amides; imides; nitriles; carbamates; alcohols; mercaptans; proteins; mixtures of amines, amides, and proteins; active methylene compounds
25 such as cyclic ketones and compounds having a β -dicarbonyl group; and heterocyclic ring compounds free of a carbonyl group and containing an NH group, with the ring made up of nitrogen or carbon atoms, the ring being unsaturated or, when fused to a phenyl group, being unsaturated or
30 saturated, and the NH group being bonded to a carbon or a nitrogen atom, which atom is directly bonded by a double bond to another carbon or nitrogen atom.

Bisulfites and sulfites useful as the formaldehyde scavenger compound in this invention include alkali metal
35 salts such as lithium, sodium and potassium salts, and ammonium salts, for example, sodium bisulfite, potassium bisulfite, lithium bisulfite, ammonium bisulfite, sodium

sulfite, potassium sulfite, lithium sulfite, ammonium sulfite, and the like.

5 Examples of amines useful in this invention include the aliphatic and aromatic amines such as, for example, aniline, benzidine, aminopyrimidine, toluene-diamine, triethylenediamine, diphenylamine, diaminodiphenylamine, hydrazines and hydrazide.

10 Suitable proteins include collagen, gelatin, casein, soybean protein, vegetable protein, keratin and glue. The preferred protein for use in this invention is casein.

Suitable amides for use in this invention include urea, cyanamide, acrylamide, benzamide, and acetamide. Urea is the preferred amide.

15 Suitable alcohols include phenols, 1,4-butanediol, d-sorbitol, and polyvinyl alcohol.

20 Examples of suitable compounds having a b-dicarbonyl group include malonic acid, acetylacetone, ethylacetone, acetate, malonamide, diethylmalonate or another malonic ester.

Preferred cyclic ketones for use in this invention include cyclohexanone or cyclopentanone.

25 Examples of suitable heterocyclic compounds for use as the formaldehyde scavenger in this invention are disclosed, for example, in U.S. Patent No. 4,127,382 (Perry) which is hereby incorporated by reference herein. Such heterocyclic compounds include, for example, benzimidazole, 5-methyl benzimidazole, 2-methylbenzimidazole, indole, pyrrole, 1,2,4-triazole, 30 indoline, benzotriazole, indoline, and the like.

A preferred formaldehyde scavenger for use in this invention is sodium bisulfite.

35 In practicing this invention, the formaldehyde concentration reducing agent, e.g., formaldehyde scavenger compound, is added in an effective amount to the cyanoacrylate. The "effective amount" is that amount sufficient to reduce the amount of formaldehyde generated

during subsequent in vivo biodegradation of the polymerized cyanoacrylate. This amount will depend on the type of active formaldehyde concentration reducing agent, and can be readily determined without undue experimentation by those skilled in the art.

The formaldehyde concentration reducing agent may be used in this invention in either free form or in microencapsulated form.

When microencapsulated, the formaldehyde concentration reducing agent is released from the microcapsule continuously over a period of time during the in vivo biodegradation of the cyanoacrylate polymer.

For purposes of this invention, the microencapsulated form of the formaldehyde concentration reducing agent is preferred because this embodiment prevents or substantially reduces polymerization of the cyanoacrylate monomer by the formaldehyde concentration reducing agent, which increases shelf-life and facilitates handling of the monomer composition during use.

Microencapsulation of the formaldehyde scavenger can be achieved, by many known microencapsulation techniques. For example, microencapsulation can be carried out by dissolving a coating polymer in a volatile solvent, e.g., methylene chloride, to a polymer concentration of about 6% by weight; adding a formaldehyde scavenger compound in particulate form to the coating polymer/solvent solution under agitation to yield a scavenger concentration of 18% by weight; slowly adding a surfactant-containing mineral oil solution to the polymer solution under rapid agitation; allowing the volatile solvent to evaporate under agitation; removing the agitator; separating the solids from the mineral oil; and washing and drying the microparticles. The size of the microparticles will range from about 0.001 to about 1000 microns.

The coating polymer for microencapsulating the formaldehyde concentration reducing agent should be

polymers which undergo in vivo bioerosion, preferably at rates similar to or greater than the cyanoacrylate polymer formed by the monomer, and should have low inherent moisture content. Such "bioerosion" can occur as a result of the physical or chemical breakdown of the encapsulating material, for example, by the encapsulating material passing from solid to solute in the presence of body fluids, or by biodegradation of the encapsulating material by agents present in the body.

Examples of coating materials which can be used to microencapsulate the formaldehyde concentration reducing agent include polyesters, such as polyglycolic acid, polylactic acid, copolymers of polyglycolic acid and polylactic acid, polycaprolactone, poly-b-hydroxybutyrate, copolymers of epsilon-caprolactone and delta-valerolactone, copolymers of epsilon-caprolactone and DL-dilactide, and polyester hydrogels; polyvinylpyrrolidone; polyamides; gelatin; albumin; proteins; collagen; poly(orthoesters); poly(anhydrides); poly(alkyl-2-cyanoacrylates); poly(dihydropyrans); poly(acetals); poly(phosphazenes); poly(urethanes); poly(dioxinones); cellulose; and starches.

Examples of the surfactant which can be added to the mineral oil include those commercially available under the designations Triton x-100, Tween 20 and Tween 80.

The composition of this invention may further contain one or more adjuvant substances, such as thickening agents, medicaments, or the like, to improve the medical utility of the monomer for particular medical applications.

Suitable thickeners include, for example, polycyanoacrylates, polylactic acid, polyglycolic acid, lactic-glycolic acid copolymers, polycaprolactone, lactic acid-caprolactone copolymers, poly-3-hydroxybutyric acid, polyorthoesters, polyalkyl acrylates, copolymers of alkylacrylate and vinyl acetate, polyalkyl methacrylates, and copolymers of alkyl methacrylates and butadiene.

To improve the cohesive strength of adhesives formed from the compositions of this invention, difunctional monomeric cross-linking agents may be added to the monomer compositions of this invention. Such crosslinking agents are known. Reference is made, for example, to U.S. Patent No. 3,940,362 to Overhults, which is hereby incorporated by reference herein. Examples of suitable crosslinking agents include alkyl bis(2-cyanoacrylates), triallyl isocyanurates, alkylene diacrylates, alkylene dimethacrylates, trimethylol propane triacrylate, and alkyl bis(2-cyanoacrylates). A catalytic amount of an amine activated free radical initiator or rate modifier is added to initiate polymerization or to modify the rate of polymerization of the cyanoacrylate monomer/crosslinking agent blend.

The compositions of this invention may further contain fibrous reinforcement and colorants, i.e., dyes and pigments. Examples of suitable fibrous reinforcement include PGA microfibrils, collagen microfibrils, cellulosic microfibrils, and olefinic microfibrils. Examples of suitable colorants include 1-hydroxy-4-[4-methylphenylamino]-9,10 anthracenedione (D+C violet No. 2); disodium salt of 6-hydroxy-5-[(4-sulfophenyl)axo]-2-naphthalene-sulfonic acid (FD+C Yellow No. 6); 9-(o-carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthen-3-one, disodium salt, monohydrate (FD+C Red No. 3); 2-(1,3-dihydro-3-oxo-5-sulfo-2H-indol-2-ylidene)-2,3-dihydro-3-oxo-1H-indole-5-sulfonic acid disodium salt (FD+C Blue No. 2); and [phthalocyaninato (2-)] copper.

The compositions of this invention can be used to join together two surfaces by applying the present composition to the surface of opposing wound surfaces that are held together. Depending on the particular requirements of the user, the adhesive compositions of this invention can be applied by known means such as with a glass stirring rod, sterile brush or medicine dropper. However, in many situations a pressurized aerosol dispens-

ing package is preferred in which the adhesive composition is in solution with a compatible anhydrous propellant.

5 In one embodiment, the present invention is directed to a method of joining together in vivo two surfaces which comprises (a) holding together tissue surfaces of a wound or incision to form an abutted tissue surface; (b) applying to said abutted tissue surface a composition of the present invention, e.g., a composition comprising 1) at least one monomer (e.g., a monomer of
10 formula (I)) which forms a medically acceptable polymer, 2) a plasticizing agent and 3) a suitable acidic stabilizing agent; and (b) maintaining the surfaces in contact until said composition polymerizes.

As above-mentioned, conventional surgical adhesive
15 compositions have been applied in very small quantities to wound surfaces before they are abutted, with care taken to remove excess adhesive. Thick films formed on wound surfaces have, in the past, resulted in increased histotoxicity of the wound tissues and increased film
20 brittleness with no increased film strength.

However, the present invention is directed to a method of joining together in vivo two tissue surfaces by applying to an already abutted tissue surface of a wound or incision a composition of this invention, preferably in
25 more than one application or coating on the abutted tissue surfaces to provide a liberal or an excess amount of the adhesive composition that is uniformly distributed on the abutted tissue surfaces. Any excess adhesive applied directly on the abutted tissue surface or on the immediate
30 vicinity of the wound or incision is preferably not removed, although excess applied to surrounding tissue not proximate to the wound region may be removed.

A subsequent coating may be applied immediately after application of a previous coating or after a
35 previous coating has been completely polymerized. Preferably, the monomer composition applied to the abutted tissue surface is allowed to at least partially polymerize

prior to subsequent coatings or applications of additional monomer composition. A coating of an adhesive composition of the present invention having a monomer different from the monomer of the first or previous coating may be applied as the second or subsequent coating. Due to the addition of the plasticizing agent and the acidic stabilizing agent, the polymer formed on the abutted tissue surface possesses sufficient bond strength and flexibility even with significant film or coating thicknesses. Suitable film thickness range from 0.1 mm to 2.0 mm or 3.0 mm or higher, preferably from 0.2 mm to 1.5 mm and more preferably from 0.4 mm to 0.8 mm.

In another embodiment, the present invention is directed to a method of joining together in vivo two tissue surfaces by application of the present adhesive composition utilizing various applicators. Such applicators include crushable swab applicators, syringes and vials with various dispensing nozzles or tips.

For example, the applicator tip may be detachable from the applicator container holding the polymerizable and/or cross-linkable material. Such an applicator tip could be attached to the applicator container prior to use and detached from the applicator container subsequent to use in order to prevent premature polymerization or cross-linking of the unapplied material in the applicator container. At this point the applicator tip may be discarded and a new applicator tip may be attached to the applicator container for subsequent use or the applicator tip may be reused.

Additionally, the applicator tip according to the present invention may comprise multiple parts, with at least one part comprising the initiator or rate modifier. For example, the component comprising the initiator or rate modifier may be fabricated separately from the other component(s) of the applicator tip and assembled prior to attachment to the applicator container.

The applicator tip may also be in the form of a nozzle for atomizing liquid polymerizable and/or cross-linkable materials. Conical, flat spray or condensed stream nozzles are suitable.

5 The applicator tip according to the present invention may be utilized in various devices. For example, manual methods of application may include utilization of hand-held devices such as syringes, adhesive guns, pipettes, eyedroppers and the like.

10 The applicator tip and the applicator container may also be an integral unit. The unit may be preformed as a single piece and charged with polymerizable and/or cross-linkable material. After application of material from the applicator container, the unit may be discarded.
15 Additionally, such an integral applicator tip/applicator container unit may be fashioned to provide the capability of recharging the unit with new material as a multiple use device.

20 The applicator tip may be composed of any of a variety of materials including polymerized materials such as plastics, foams, rubber, thermosets, films or membranes. Additionally, the applicator tip may be composed of materials such as metal, glass, paper, ceramics, cardboard and the like. The applicator tip
25 material may be porous, absorbent or adsorbent in nature to enhance and facilitate loading of the initiator or rate modifier on or within the applicator tip. For example, the applicator tip may be composed of a material having random pores, a honey-comb material, a material having a
30 woven pattern, etc. The degree of porosity will depend on the materials being used.

 In embodiments, the applicator tip may be porous and have an average pore size of about 1 μm to about 500 μm . Generally, according to the present invention, an
35 applicator tip having an average pore size of about 20 μm is used with a polymerizable material having a viscosity of about 7 cPs at 25°C. When polymerizable and/or cross-

linkable material has a viscosity higher than 7 cPs, the average pore size of the applicator tip is generally increased. For example, an applicator tip having an average pore size of about 140 μm is preferably used with
5 a polymerizable material having a viscosity of about 250 cPs at 25°C. Porosity is the open volume within the pores of an applicator tip divided by the total volume of the applicator tip. In embodiments, an applicator tip has a porosity of less than or equal to 80 percent.

10 The applicator tip according to the present invention, where it connects to the applicator container, may have an elongated tubular portion, out of which the mixed polymerizing and/or cross-linking material is expelled. A portion of the applicator tip which is
15 immediately downstream of the applicator container is advantageously porous in order to avoid a sharp pressure drop and ensure a constant mixed ratio profile. The structure can preferably trap any barriers or materials used to separate multiple components within the applicator
20 container. Thus, any such barriers will not clog the device.

Initiators that initiate polymerization and/or cross-linking of the material, or rate modifiers that modify the rate of polymerization of the material, may be
25 applied to a surface portion or to the entire surface of the applicator tip, including the interior and the exterior of the tip. Alternatively, the initiator or rate modifier may be coated only on an internal surface of the applicator tip. Preferably, only a portion of the
30 interior of the applicator tip is coated with the initiator or rate modifier.

The initiator or rate modifier on the applicator tip may be in the form of a solid, such as a powder or a solid film, or in the form of a liquid, such as a viscous
35 or paste-like material. The initiator or rate modifier may also include a variety of additives, such as surfactants or emulsifiers. Preferably, the initiator is

soluble in the polymerizable and/or cross-linkable material, and/or comprises or is accompanied by at least one surfactant which, in embodiments, helps the initiator co-elute with the polymerizable and/or cross-linkable material. In embodiments, the surfactant may help solubilize the initiator in the polymerizable and/or cross-linkable material.

Particular initiators for particular systems may be readily selected by one of ordinary skill in the art without undue experimentation. Suitable initiators include, but are not limited to, detergent compositions; surfactants: e.g., nonionic surfactants such as polysorbate 20 (e.g., Tween 20TM), polysorbate 80 (e.g., Tween 80TM) and poloxamers, cationic surfactants such as benzalkonium chloride and tetrabutylammonium bromide, anionic surfactants such as sodium tetradecyl sulfate, and amphoteric or zwitterionic surfactants such as dodecyldimethyl(3-sulfopropyl)ammonium hydroxide, inner salt; amines, imines and amides, such as imidazole, tryptamine, urea, arginine and povidine; phosphines, phosphites and phosphonium salts, such as triphenylphosphine and triethyl phosphite; alcohols such as ethylene glycol, methyl gallate, ascorbic acid, tannins and tannic acid; inorganic bases and salts, such as sodium bisulfite, magnesium hydroxide, calcium sulfate and sodium silicate; sulfur compounds such as thiourea and polysulfides; polymeric cyclic ethers such as monensin, nonactin, crown ethers, calixarenes and polymeric epoxides; cyclic and acyclic carbonates, such as diethyl carbonate; phase transfer catalysts such as Aliquat 336; organometallics such as cobalt naphthenate and manganese acetylacetonate; and radical initiators and radicals, such as di-t-butyl peroxide and azobisisobutyronitrile. The polymerizable and/or cross-linkable material may also contain an initiator which is inactive until activated by a catalyst or accelerator (included within the scope of the term "initiator" as used herein) in the applicator

tip. Initiators activated by stimulation such as heat and/or light (e.g., ultraviolet or visible light) are also suitable if the tip and/or applicator is appropriately subjected to such stimulation.

5 The initiator or rate modifier may be applied to the surface of the applicator tip or may be impregnated or incorporated into the matrix or internal portions of the applicator tip. In embodiments, when using a porous applicator, the amount of initiator or rate modifier
10 necessary to initiate and/or to modify the rate of polymerization and/or cross-linking increases as the pore size of the applicator tip increases. The initiator or rate modifier may be applied to the applicator tip by spraying, dipping, or brushing the applicator tip with a
15 liquid medium containing the initiator or rate modifier. The liquid medium may include non-aqueous solvents, such as ether, acetone, ethanol, pentane or mixtures thereof; or may include aqueous solutions. Preferably, the liquid medium is a low boiling point solvent.

20 In some embodiments of the present invention, the distribution of initiator or rate modifier may be uniform within the applicator tip. In other embodiments, there may be an anisotropic distribution or concentration gradient of initiator or rate modifier in the applicator
25 tip. In embodiments, the concentration gradient may increase or decrease from the beginning of the applicator tip to the end of tip. The distribution of the initiator or rate modifier may be varied depending on the solvent used to apply the initiator and the wetting
30 characteristics desired.

 Suitable applicators for application of the adhesive of the present invention include those described in copending Application Serial No. 08/488,411, the subject matter of which is incorporated herein by
35 reference. A preferable applicator is a crushable swab applicator.

Specific methods which may use an adhesive composition of the present invention include methods for repairing damaged living tissue to prevent the escape of fluids therethrough by holding damaged tissue edges together in an abutting relationship, applying to the abutting tissue the monomer composition of the present invention, and allowing the composition to polymerize; and methods for stemming the flow of blood from vessels which comprises holding damaged regions of the blood vessels together, applying the present monomer composition to the damaged regions and allowing the composition to polymerize.

When using a porous applicator tip to apply the adhesive composition, the composition preferably is not expressed directly through the applicator tip in a continuous motion. According to embodiments of the present invention, the adhesive composition is (1) expressed to the end or part way to the end of the applicator tip, (2) the pressure is released to draw the composition back into the applicator, and (3) the composition is then subsequently expressed through the applicator tip in a continuous motion. This is called a suck-back method of applying the adhesive composition of the present invention. As a result, the adhesive composition polymerizes more slowly than if it had been expressed directly through the tip.

Repairing injured tissues (for example, to control bleeding) comprises, in general, sponging to remove superficial body fluids, holding injured tissue surfaces together in an abutting relationship and subsequent application to the exposed abutted tissue of the present adhesive composition. The composition polymerizes to a thin film of polymer while in contact with the abutted tissue surface. Tissues which are not bleeding or otherwise covered by body fluids need not be sponged first. More than one coating or application of monomer composition may be applied to the abutted tissue surface.

The monomers are readily polymerized to addition-type polymers and copolymers, which are generally optically clear (as films).

5 In most bonding applications using the compositions of this invention, polymerization of the monomers is catalyzed by small amounts of moisture on the surface of the adherents. Similarly, polymerization rate modifiers are catalyzed by small amounts of moisture. Thus, desired bonding of tissues or hemostasis proceeds
10 well in the presence of blood and other body fluids. The bonds formed are of adequate flexibility and strength to withstand normal movement of tissue. In addition, bond strength is maintained as natural wound healing proceeds.

Compositions employed in the invention are
15 preferably sterilizable by conventional methods that include, but are not limited to, autoclave or aseptic filtration techniques.

EXAMPLES I-VI

The compositions according to the present
20 invention are prepared utilizing conventional mixing equipment. For example, the process may be conducted as follows:

To a surgical grade cyanoacrylate in a round-bottom flask is added the plasticizer, the acidic
25 stabilizer, and other formulation components as described herein. The resulting mixture is mechanically stirred until it is homogeneous.

The invention is further illustrated by the following non-limiting examples.

30 In the following examples, various amounts of plasticizer (i.e., acetyl tributyl citrate) are utilized in adhesive compositions of the present invention that illustrate the effects on the strengths of the bonds formed by the adhesive.

35 The data presented in Table I is generated using the following method:

1. A 2" incision is made in a 5 1/2" x 5 1/2" sheet of latex (1/16" thickness).
2. An adhesive composition (i.e., 2-octyl cyanoacrylate) is applied topically to the incision with a crushable swab with a polymerization initiated tip. The interface of the incision must not be inadvertently glued.
3. After curing for one hour, the sheet is fixed between two sheets of plexiglass. The bottom sheet is equipped with a pressure transducer and gas inlet. The upper sheet has a 3 5/8" hole centrally located in it. The test piece is positioned such that the glued side is facing the upper sheet of plexiglass containing the 3 5/8" hole.
4. The valve controlling gas flow is opened to pressurize the test material. Pressure is increased until failure.
5. Peak pressure is recorded by the transducer and recorded on a chart recorder. Ten determinations per test material are made.

The results are as follows:

TABLE I:

EXAMPLE	Concentration(w/w%) of Plasticizer	BURST PRESSURE (psi)
I	0.0	3.9
II	5.7	3.9
III	9.1	3.7
IV	15.2	3.2
V	20.0	2.6
VI	25.9	2.1

EXAMPLES VII-X

5 In order to demonstrate the unexpected superiority of the in vivo film strength provided by the adhesive composition and application method according to the present invention, various methods and materials for wound closure and topical administration of various surgical wound closure devices are evaluated (Examples VII-X). In vivo strength is objectively defined by the amount of
10 ultimate pressure required to induce wound failure (i.e., the amounts of vacuum pressure required to open the wound). The biomechanical analysis is performed using the Dimensional Analysis Systems (DAS), (DIMENSIONAL ANALYSIS SYSTEMS, LEONIA, NEW JERSEY). This technology is
15 specifically designed for objective in vivo biomechanical characterization of linear incision wounds. In contrast to previous biomechanical analysis methods (e.g., uniaxial tensiometers), the DAS applies a multi-axial stress to a wound which is more analogous to stresses experienced in
20 clinical conditions. Moreover, the DAS does not require tissue manipulation or destructive incision of specimens prior to testing. Therefore, sensitive, reliable and reproducible measurements of fragile wounds may be obtained in the early phases of healing. The DAS further
25 eliminates the artifact error and the experimental variables introduced by excisional methods such as, non-viable tissue samples, inconsistent variation of sample dimensions, and flawed edges from excising tissues.

30 The male Sprague Dawley rat is selected for the animal model because of its genetic homogeneity, ease of handling and housing, and overall popularity as a linear incision wound model, thus allowing comparison of data to other similar studies. This model has been used extensively in incisional wound research, which is well
35 documented in the literature.

Male Sprague Dawley rats, purchased from Harlan Sprague Dawley, Inc. (Indianapolis, Indiana) are utilized

in the tests. All animals are held seven days prior to the procedures for stabilization of diet and behavior. Four groups of rats (Groups A-D), each with a different wound closure method and/or surgical adhesive, are tested under identical conditions. Each of the specimens are tested for film strength one hour after closure of the linear incision wounds.

EXAMPLE VII

In the first group of rats, designated as Group A, a one-stroke technique for application of tissue adhesive is employed. An adhesive of the present invention containing about 6% by weight of plasticizer with acetic acid as an acidic stabilizer ($pK_a=4.8$) in 2-octyl alpha-cyanoacrylate is applied with a compressible ampule with a swab tip (crushable swab applicator) and is passed along the opposing wound edges in a "one-stroke" fashion for topical administration.

EXAMPLE VIII

In the second group of rats, designated as Group B, linear incisions are closed with the same adhesive using a multi-stroke technique. The adhesive is applied with a compressible ampule passed more than once along the opposing wound edges in a "multi-stroke" fashion, resulting in 2-3 distinct applications of adhesive.

EXAMPLE IX

In the third group of rats, designated as Group C, linear incision wounds are closed with the same adhesive using a minimal surface exposure technique. Adhesive is applied with a UniJect™ syringe (available from Horizon, Santa Ana, CA, USA) with approximately 3-4 drops in an attempt to limit the amount of adhesive exposed to the skin surface, thus administering the adhesive to the opposing wound edges only.

EXAMPLE X

In the fourth group of rats, designed as Group D, linear incision wounds are closed with Histoacryl® (a

surgical adhesive available from B. Braun Melsungen AG of Germany) using the application technique of Example IX.

The results from the in vivo biomechanical analyses are displayed in Table II below. As illustrated in Table II, there are significant differences observed between all groups at the one hour time period studied. Group B, the multi-stroke technique, demonstrates a significant increase in ultimate pressure in comparison to Groups A & C. This data suggests that increasing the amount of adhesive applied may allow for higher in vivo strength. Group D reveals a highly significant decrease in in vivo strength in comparison to all groups evaluated.

TABLE II:

Reveals statistical results for direct comparisons of the alternate methods and other techniques at 1 hour post-application.

Group	Number of Incisions	<u>In Vivo</u> strength (mmHg)
A:one stroke	10	110.30
B:multi-stroke	10	214.57
C:minimal surface exposure	10	94.36
D:Histoacryl (minimal surface exposure)	10	62.80

EXAMPLE XI

The efficacy of the same tissue adhesive according to the present invention is tested in its ability to close skin incisions in a pig model. The tissue adhesive, Histoacryl®, is used as a control.

Incisions are made on each side of the back of these pigs with sterile scalpel blades at a controlled depth for the incisions. The incisions are closed either with the test material or with the control. The same adhesive of the present invention, incorporated into an applicator, was applied onto the opposed abutted edges of

the wound until the adhesive polymerizes (i.e., the adhesive is no longer sticky to the touch). The applicator is a transparent, flexible, plastic cylinder with an absorbent head (crushable swab). Within the cylinder is a glass vial containing the adhesive which is broken by squeezing the cylinder. As the applicator is inverted, the adhesive is squeezed out of the cylinder into the head and then onto the skin. Histoacryl® is also applied with an applicator, which is a sealed plastic ampule with a narrow neck. The ampule is attached to a 27 gauge hypodermic needle. The ampule is inverted and the adhesive is applied by squeezing the ampule and dripping microdrops from the end of the needle onto the opposed edges of the incision. Care is taken not to touch the skin with the needle tip. The method of applying Histoacryl® has been described by J. Quinn and J. Kissick (1994, "Tissue adhesives for laceration repair during sporting events", Clin. J. Sport Med., 4:245-248).

Observations are made frequently during the recovery phase, recorded approximately four hours postoperatively, and then daily to determine if any of the incisions partially or completely separates (dehiscence), and if there are any adverse tissue responses. If a wound opens during the observation period, it is not reclosed.

TABLE III

DEHISCENCE OF PIG SKIN INCISIONS

	Invention™	Histoacryl™
<u>FIG 1</u>		
Number of incisions	4	4
Number of partial or complete dehiscences	0	1
<u>FIG 2</u>		
Number of incisions	4	4
Number of partial or complete dehiscences	0	4
<u>FIG 3</u>		

number of incisions	4	4
Number of partial or complete dehiscences	0	2

5 The pigs are observed for wound dehiscence for 10 days. Dehiscence is not observed in any incision closed with the adhesive of the invention. Partial or complete dehiscence is observed in 7 of the 12 incisions closed with Histoacryl®. Complications such as infection or necrosis are not observed.

WHAT IS CLAIMED IS:

1. A method of joining together surfaces, comprising:

5 (a) holding together at least two surfaces to form abutted surfaces,

(b) applying across said abutted surfaces an excess amount of an adhesive composition that is uniformly distributed comprising at least one monomer that forms a polymer with an applicator having a porous applicator tip; and

10

(c) maintaining said abutted surfaces in contact until said composition polymerizes to form a thick film of polymerized composition on said abutted surfaces.

15 2. The method according to claim 1, wherein said surfaces are in vivo living tissue surfaces and said monomer forms a medically acceptable polymer.

3. The method according to claim 2, wherein said applicator tip has an average pore size of about 1 μm to about 500 μm .

20

4. The method according to claim 2, wherein said applicator tip has an average pore size of about 20 μm and said composition has a viscosity of about 7 cPs at 25°C.

25 5. The method according to claim 2, wherein said applicator tip has a porosity of less than or equal to 80 percent.

6. A method according to claim 2, wherein said adhesive composition comprises:

30 at least one monomer, which forms a medically acceptable polymer;

at least one plasticizing agent present in the composition in an amount of from 0.5 wt.% to 16 wt.% of the composition; and

35 at least one acidic stabilizing agent having a pK_a ionization constant of from about 0 to about 7.

7. A method according to claim 2, wherein more than one application of said adhesive composition is provided across said abutted tissue surfaces.

5 8. A method according to claim 7, wherein said adhesive composition applied across said abutted tissue surfaces is allowed to at least partially polymerize prior to subsequent coatings or applications of said adhesive composition.

10 9. A method according to claim 7, wherein an adhesive composition having a monomer different from the monomer of a previous coating is applied as a subsequent coating.

15 10. A method according to claim 2, wherein said adhesive composition polymerizes to form a bridge across said abutted tissue surfaces.

11. A method according to claim 2, wherein said thick film has a thickness of 0.1 mm to 3.0 mm.

12. An *in vivo* film formed across abutted tissue surfaces made by the method of claim 2.

20 13. The method according to claim 2, wherein said applicator tip comprises a polymerization or cross-linking initiator or rate modifier for said adhesive composition.

25 14. The method according to claim 1, wherein said applicator tip is integral with said applicator.

15. The method according to claim 1, wherein said applicator is selected from the group consisting of a syringe, a flexible cylinder, a tube, a pipette and an eyedropper.

30 16. The method according to claim 2, wherein said at least one monomer is located in said applicator in a non-contacting relationship with said porous applicator tip prior to dispensing said adhesive.

35 17. The method according to claim 2, wherein said applying step comprises:

applying pressure to express said composition to an end or part way to an end of said applicator tip;

releasing pressure to draw said composition back into said applicator; and

subsequently reapplying pressure to express said composition through said applicator tip in a continuous motion.

18. The method according to claim 13, wherein said initiator or rate modifier is anisotropically distributed in said applicator tip.

19. The method according to claim 13, wherein said applicator tip comprises a concentration gradient of said initiator or rate modifier.

20. A method of forming a biocompatible film across abutted tissue surfaces, comprising

(a) holding together at least two tissue surfaces to form abutted tissue surfaces,

(b) applying across said abutted tissue surfaces an adhesive biocompatible monomer composition with an applicator having a porous applicator tip, and

(c) allowing said composition to polymerize and form a biocompatible film on said abutted tissue surfaces having an in vivo film strength of at least 70 mmHg of pressure required to induce wound failure.

21. A method according to claim 20, wherein said in vivo film strength is at least 90 mmHg of pressure required to induce wound failure.

22. A method according to claim 20, wherein said in vivo film strength is at least 100 mmHg of pressure required to induce wound failure.

23. A device for dispensing a polymerizable or cross-linkable monomer material from an applicator, comprising a porous applicator tip with an average pore size of about 1 μm to about 500 μm .

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/17708

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40797 A (TRI POINT MEDICAL CORP) 19 December 1996	1-5, 7-23
Y	see page 5, line 33 - page 6, line 2 see page 7, line 23 - page 8, line 5 see page 19, line 5 - line 34 see claims 1, 3, 4, 13, 17	6
Y	US 5 480 935 A (GREFF RICHARD J ET AL) 2 January 1996 cited in the application see column 2, line 31 - column 4, line 34	6
P, Y	WO 97 31598 A (CLOSURE MEDICAL CORP) 4 September 1997 see abstract	6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

5 January 1999

Date of mailing of the international search report

14/01/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Heck, G

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/17708

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 2-13, 16-22
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 2-13, 16-22
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition. (Rule 39.1(iv) PCT)
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/17708

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 2-13,16-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 98/17708

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9640797	A	19-12-1996	AU 6262696 A	30-12-1996
			CA 2221260 A	19-12-1996
			CN 1186503 A	01-07-1998
			EP 0832137 A	01-04-1998
US 5480935	A	02-01-1996	CA 2198486 A	07-03-1996
			EP 0778863 A	18-06-1997
			JP 10508326 T	18-08-1998
			WO 9606884 A	07-03-1996
			US 5665817 A	09-09-1997
WO 9731598	A	04-09-1997	AU 1981497 A	16-09-1997
			EP 0886507 A	30-12-1998